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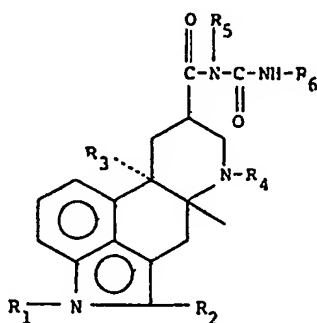
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(54) Ergoline derivatives

(57) A process is provided for preparing ergoline derivatives I



R<sub>1</sub> = H or CH<sub>3</sub>  
R<sub>2</sub> = H, halogen or CH<sub>3</sub>  
R<sub>3</sub> = H or CH<sub>3</sub>O  
R<sub>4</sub> = C<sub>1</sub> - C<sub>4</sub> hydrocarbon  
R<sub>6</sub> = C<sub>1</sub> - C<sub>4</sub> alkyl, cyclohexyl,

substituted phenyl, unsubstituted phenyl, (CH<sub>2</sub>)<sub>n</sub> N(CH<sub>3</sub>)<sub>2</sub> wherein *n* is an integer,  
R<sub>5</sub> = any of values of R<sub>6</sub> or H, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, thiazolyl or  
thiadiazolyl.

The process comprises condensing an ergoline amide (I; 8-substituent replaced  
by CONHR<sub>5</sub>) with R<sub>6</sub>-N=C=O in a solvent at 70°C to 120°C for 24 to 72 hours.

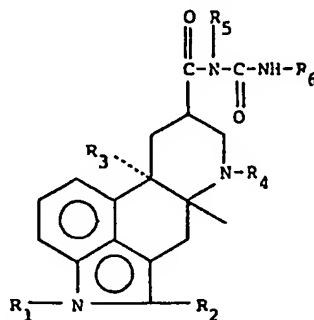
## SPECIFICATION

## Ergoline derivatives

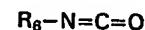
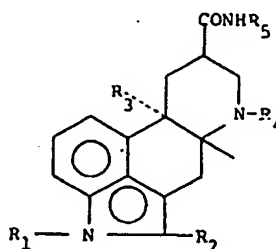
## 5 Description

The invention relates to a process for the preparation of ergoline derivatives.

The invention provides a process for the preparation of ergoline derivatives of the general formula I



wherein  $R_1$  represents a hydrogen atom or a methyl group,  $R_2$  represents a hydrogen or halogen atom or a methyl group,  $R_3$  represents a hydrogen atom or a methoxy group,  $R_4$  represents an hydrocarbon group having from 1 to 4 carbon atoms,  $R_5$  represents an alkyl group having from 1 to 4 carbon atoms, a cyclohexyl group or a substituted or unsubstituted phenyl group or a dimethylamino alkyl group  $(CH_2)_nN(CH_3)_2$  in which  $n$  is an integer,  $R_6$  represents any of the groups which  $R_5$  may represent or a hydrogen atom or a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, thiazolyl or thiadiazolyl residue, the process comprising reacting an ergoline amide of the general formula II with an isocyanate of the general formula III



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wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  have the above given meanings. The reaction is suitable carried out at a temperature of from 70 to 120°C in solvents such as dioxan, benzene, toluene, cyclohexane or the like for a period of from 24 to 72 hours. At the end of the reaction the products may be isolated and purified following conventional procedures, for example chromatography and/or crystallization and salt formation.

The starting materials which are employed in the process according to the invention are known compounds or may be prepared by established procedures starting from known compounds; moreover some compounds of formula II are described in our British Patent Applications Nos 8122356 and 8209544, in our Belgian Patent No 888243, in our German Patent Application No 3112861 and in our Japanese Patent Application No. 81/48491.

The preparation of some compounds of general formula I is described in our British Patent Application No. 2074566A. Although the process there described is capable of producing derivatives of the general formula I in which the groups represented by  $R_5$  and  $R_6$  are the same in good yields its practical value is reduced when used to prepare compounds of the general formula I wherein the groups represented by  $R_5$  and  $R_6$  are different. In this case both regioisomers are obtained and the yields of the isolated products are often low as a consequence of the isolation difficulties. The process of the present invention proved most practicable because it is regiospecific and eliminates the above mentioned difficulties and because it allows the preparation of certain biologically active compounds which could not be obtained, owing to the instability of the required carbodiimides, with the process previously described in British Patent Application No. 2074566A.

The following Examples illustrate the invention.

## EXAMPLE 1

6-Allyl-8β-(1-ethyl-3-(3-dimethylaminopropyl)-ureidocarbonyl)-ergoline

I:  $R_1=R_2=R_3=H$ ,  $R_4=allyl$ ,  $R_5=(CH_3)_2N.CH_2CH_2CH_2$ ,  $R_6=C_2H_5$

A mixture of 20 g of 6-allyl-8β-(3-dimethyl-aminopropyl-carbamoyl)-ergoline (m.p. 198-200°C) and 150 ml of ethyl isocyanate in 1000 ml of toluene were refluxed for 72 hours. The resultant solution was distilled at 70-80°C and at 30 mm pressure; the residue was applied to a chromatographic column packed with 60 g of kieselgel (0.05-0.2 mm) and eluted with acetone. Eluate fractions shown to contain the product were combined and the solvent was removed therefrom under reduced pressure to give 20 g of the title compound as foam: m.p. 152-154°C as its disphosphate salt.

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## EXAMPLE 2

6-Allyl-8β-(1-ethylureidocarbonyl)-ergoline

I:  $R_1=R_2=R_3=R_5=H$ ,  $R_4=allyl$ ,  $R_6=C_2H_5$

Operating as in Example 1, but employing 6-allyl-8β-carbamoyl-ergoline (m.p. 190-193°C) instead of 6-allyl-8β-(3-dimethylaminopropyl-carbamoyl)-ergoline, the title compound, m.p. 210-212°C, was obtained in 90% yield.

## EXAMPLE 3

6-Allyl-8β-(1,3-dimethylureidocarbonyl)-ergoline

20 I:  $R_1=R_2=R_3=H$ ,  $R_4=allyl$ ,  $R_5=R_6=CH_3$

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Operating as in Example 1, but employing 6-allyl-8β-methylcarbamoyl-ergoline instead of 6-allyl-8β-(3-dimethylaminopropyl-carbamoyl)-ergoline and methyl isocyanate instead of ethyl isocyanate, the title compound, m.p. 106-108°C, was obtained in 87% yield.

## 25 CLAIMS

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1. A process for the preparation of an ergoline derivative of the general formula I as herein defined, the process comprising reacting an ergoline amide of the general formula II as herein defined with an isocyanate of the general formula III as herein defined in a solvent at from 70°C to 120°C for from 24 to 72 hours.
2. A process according to claim 1 in which the solvent is dioxan, benzene, toluene or cyclohexane.
3. A process for the preparation of an ergoline derivative of the general formula I as herein defined, the process being substantially as described herein with reference to any of the Examples.

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